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MORPHOFUNCTIONAL CHANGES OF THE MYOCARDIUM OF RATS AFTER THE EFFECT OF GENERAL AND LOCAL HYPOTHERMIA

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The results of the research at the microscopic level, after the effect of general hypothermia with a duration of exposure of 10 days, an increase in the size of cardiomyocytes, the interstitial space was found, which indicated the activation of adaptive processes of the microcirculatory bed and the energy supply apparatus of cells that occur in cardiomyocytes under the effect of general hypothermia with an early duration of action; with a term of action of 30 days – marked defibrillation of muscle fibers in the myocardium of the heart of the ventricles and the interventricular membrane of rats. The effect of local hypothermia using a cardioplegic solution for cooling the heart allows you to preserve the typical structure of the myocardium, while protecting the structural organization. Dry cooling of the heart causes destructive changes in the myocardium with the development of degenerative and destructive processes in the myocardium of the heart, in places muscle fiber breaks, myofibrils defibration, their destruction and an increase in intercellular spaces, which indicates the depressing effect and irreversible damage of this method of local hypothermia (dry cold) on the myocardium of the ventricles and interventricular membrane.

Key words: *heart, myocardium, thyroid gland, hypothyroidism, microwave electromagnetic radiation.*

Connection of the publication with planned research works. The research was carried out within the framework of the scientific topic of the department of human anatomy, clinical anatomy and operative surgery «Morphofunctional state of organs and tissues of experimental animals and humans in ontogenesis in normal and under the influence of external and internal factors», № state registration 0117U003181.

Introduction. According to the literature, the effects of some chemicals and hypothermia, in general, have been experimentally determined. Still, the effects of local and general hypothermia on the morphogenesis of the heart, especially under conditions of cooling, remain unexplored [1]. As for the influence of hypothermia, such an important question arises as the concepts of local and general cooling significantly impact the heart's morphogenesis. Direct observation of the effect of hypothermia on the structures of the heart in humans is impossible; therefore, with the help of induced experimental models, it becomes possible to analyze the morphological changes of the heart after exposure to cooling [2]. During the research, the role of modeling the pathological state, identifying the terms, causes, and mechanism of the formation of disturbances in the morphogenesis of the heart, its wall, and structural elements or components is increasing, which makes it possible to develop a model of hypothermia and will help to determine the corrective measures of cooling action. In the available literature, we could not find comprehensive studies using electrophysiological, general histological methods, immunohistochemistry, and electron microscopy of the myocardium in the pathology mentioned above [3, 4].

This substantiates the relevance of this research and the expediency of conducting it. According to the literature, hypothermia is when the internal body temperature drops below 35 degrees Celsius. Moderate therapeutic hypothermia procedures are used in post-cardiac arrest treatment, while surgical procedures often use lower core temperatures to provide cerebral protection [5]. An involuntary decrease in internal body temperature occurs with accidental hypothermia, and ventricular arrhythmias are considered the main cause of high mortality in these patients. Hypothermia is a relatively common clinical condition that is associated with significant morbidity and mortality, especially if it is not recognized and treated in time. This condition, associated with extreme changes in the body's internal temperature, can be accompanied by a violation of cardiac function, often with the apparent difference in the electrocardiogram [6, 7]. Many researchers are engaged in studying the morphology of organs under therapeutic effects, but the morphological modifications of these organs under

Table – Distribution of material of control and experimental groups

The name of the experimental groups	Control	General hypothermia 10 days	General hypothermia 30 days	Cardioplegic solution	In the dry cold
	Group 1	Group 2	Group 3	Group 4	Group 5
Total objects: 100 (100%)	27 25,0%	27 25,0%	27 25,0%	27 25,0%	27 25,0%

the influence of non-lethal hypothermia remain undescribed. In this connection, the study of the effect of hypothermia is an urgent issue, both for theoretical and practical medicine.

The purpose of the study. To determine the morphological features of the heart wall after exposure to general and local hypothermia.

Object and methods of research. The object of the study was the hearts of laboratory sexually mature rats weighing 180-220 g, aged 6-8 months. 135 animals were involved in the study. Experimental animals were divided into 5 groups of 27 objects, which was 25.0% **(table)**.

The animals were to be cooled in a refrigerating chamber for 3 hours daily for ten and thirty days, at a temperature of -10^{0}C. After withdrawal from the experiment, a histological and morphometric study of rat hearts was performed **(fig. 1)**.

Research results and their discussion. To establish the shape of the heart and trace dynamic changes at the organ level, we calculated an index showing the ratio of the width of the heart to its length (F). In 80% of cases, the shape of the heart of rats in the control group was cone-shaped; the index (F) was on average 55%, only in 20% it was elliptical, the index was more than 65%. We did not observe other forms of the heart in the control group of rats. A ball-shaped heart shape appeared in the experimental groups **(fig. 2)**. In our study of the rat heart, we determined macro-level changes in weight and mass metric parameters of rat hearts and rats, in general, to calculate the percentage ratio of heart weight to rat weight index – J index after exposure to general hypothermia in the early – 10 day and late – 30 day periods – compared to the control group. The highest index of the ratio of the weight of the heart to the weight of the rats was noted in rats with general hypothermia. After exposure to general hypothermia in the early stages – the 10th day, the index of the ratio of the weight of the heart to the weight of the rat was equal to 0.56. After exposure to general hypothermia in the late period on the 30th day, these indicators changed more clearly in comparison with the control group, where the index was equal to 0.32, and in comparison with the group of general hypothermia, but in the early period. The index of the ratio of heart mass to rat weight on the 30th day was 0.75 **(fig. 3)**.

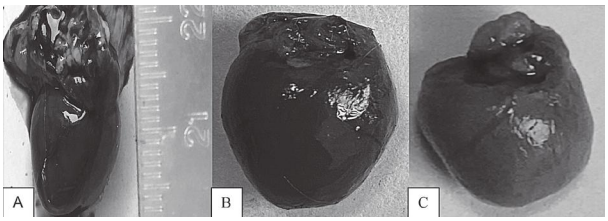

Figure 1 – Hearts of rats in the control group (A) and after exposure to general hypothermia in the early (B) and late (C) periods.

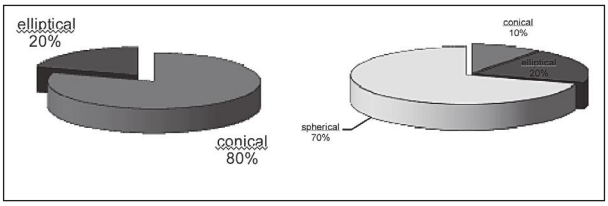

Figure 2 – Distribution of rats according to the shape of the heart of the control group and after hypothermia.

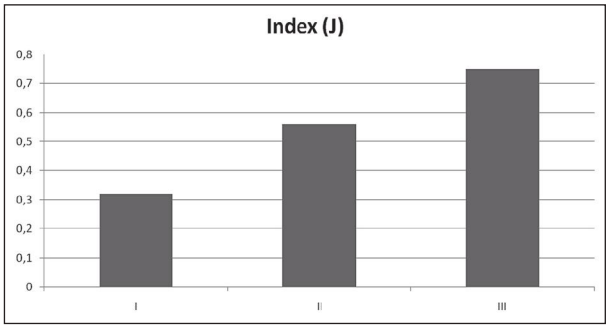

Figure 3 – J index (heart weight/rat weight).

After exposure to general hypothermia in the experimental group, histological sections in the myocardium showed the formation of cavities of an irregular oval and spherical shape with a diameter equal to 1-2 to 5-6 diameters of cardiomyocytes, swelling of cardiomyocytes, interstitial space, as well as hyperemia of blood vessels and swelling of their endothelium **(fig. 4)**.

In our study of rat hearts, we measured the thickness of the cardiac wall in different parts of the heart: in the left ventricle, the thickness of the anterior wall, the lateral wall, and the posterior wall at three levels. The right ventricle has the thickness of the front and the back walls and three sizes of the interventricular membrane. At all levels of the cross-section of both the right and left ventricles, the highest values after exposure to general hypothermia in the early and late periods were noted in the middle third of the heart (zone "B"). Indicators in the middle third of the left ventricle were on average 31% more than the indicators in the area of the base of the heart, and 56% more than in the lower third. In the right ventricle, these indicators were equal in the base area by 22%, and in the lower third area by 2% **(fig. 5)**.

The thickness of the front wall of **the left ventricle** on the 10th day from the beginning of the experiment was 3.15±0.11 mm, the side wall 3.1±0.11 mm, the back wall 2.45±0.04 mm, the interventricular membrane 2.95±0 .09 mm. On the 30th day from the beginning of the experiment, the thickness of the front wall of the left ventricle was equal to 3.21±0.11 mm, the side wall 2.65±0.06 mm, the back wall 3.27±0.09 mm, the interventricular membrane 3.14±0, 13 mm **(fig. 6)**. In **the right ventricle**, on the 10th day of the general hypothermia experiment, the thickness of the front wall was 1.04±0.03 mm, the back wall was 1.36±0.04mm, on the 30th day, the thickness of the front wall was 1.09±0.04mm, of the back wall 1.38±0.03 mm **(fig. 7)**.

Our studies of the myocardium of the heart wall of rats using electron microscopy showed that this method allows us to evaluate the processes of heart remodeling after hypothermia and confirm the completeness of the structure of the studied objects. When studying the structures of the myocardium obtained after hypother-

mia for 10 days, it was observed that the mitochondrial apparatus of contractile cardiomyocytes of the left ventricle did not reveal significant differences between this experimental group and animals of the control group.

The presence of polymorphic mitochondria characterized the subsarcolemmal zone of cardiomyocytes. Among them were large-volume organelles with an elongated or spherical shape, an ordered orientation of the cristae, and a moderately dense matrix. The organelles were determined to be smaller in volume, by developing the outer and inner mitochondrial membranes and the number of weakly oriented cristae. There were also small-sized mitochondria, the number, and the cristae density, which significantly exceeded similar indicators of other types of mitochondria. The para nuclear zone of contractile myocytes was represented mainly by mitochondria with ultrastructural signs of moderate functional activity: small-sized spherical organelles with a lighted matrix and a small number of low-density, poorly oriented cristae.

Many neighboring mitochondria were in contact with each other via intramitochondrial connections. Sometimes the outer mitochondrial membrane in the area where the two organelles fit was completely absent. In this place, an intramitochondrial bridge connected the matrix of both mitochondria. Such bridges were located at the level of Z-lines of myofibrils. The study of mitochondria near the nucleus showed that the irregularly organized organelles formed more contacts than the orderly located mitochondria of the intermyofibrillar zone **(fig. 8-A)**. No damage was observed in the structure of the outer mitochondrial membrane. Mitochondria dominated the spaces between myofibrils with signs of structural and functional overload. Along with this, numerous newly formed micro mitochondria were observed in large numbers. Small-sized mitochondria represented organelles of para nuclear localization with a light matrix and disordered cristae. Among the changed organelles, there were mitochondria with signs of overvoltage: areas of uneven illumination of the matrix, with phenomena of cristae destruction. An insignificant number of intramitochondrial contacts was detected between such mitochondria. In the subsarcolemmal zone, the organelles had a spherical or elongated shape, a transparent matrix; among them were significantly swollen mitochondria, organelles with destroyed cristae, and areas of sharp lightening of the matrix. There were few intramitochondrial contacts. Mitochondria located between myofibrils were large, with moderately developed cristae and a transparent matrix. Among such organelles, organelles with elements of crystallization and zones of sharp lightening of the matrix predominated **(fig. 8-B)**. Mitochondria of gigantic size were sometimes found due to sharp swelling of the matrix. Newly formed micro mitochondria against the background of destructive and degenerative processes were found in small numbers in the form of small spherical formations with single cristae, mainly near the nucleus **(fig. 9)**.

To study the myocardium of rats on the 30th day of the experiment, we used LC3B immunohistochemical markers. The accumulation of this marker in the myocardium increased on the 30th day of the experiment, which indicated active autophagy processes **(fig. 10-A, B)**.

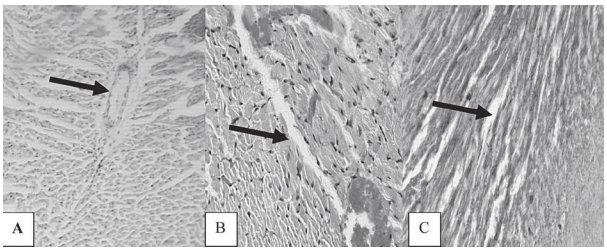

Figure 4 – Myocardium of a rat of the control group (A) and after general hypothermia (B, C). Hematoxylin – eosin staining. Magn.: Ob. 10. approx. 4.

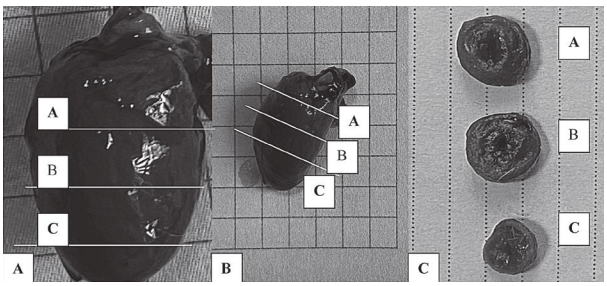

Figure 5 – The heart of a rat with the specified measurement lines (A – the base of the heart, B – the middle third of the heart, C – the lower third of the heart) – A, B.

And also the marker of endothelial dysfunction e NOS, the accumulation of which also increased up to the 30th day of the experiment **(fig. 11-A, B)**. After hypothermia, we observed a decrease in the amplitude and an increase in the duration of the complex, which indicated hypoxic damage to the myocardium. We also marked the appearance of a J wave (the Osborne wave), which appears during hypothermia. We also recorded action potentials, an ECG on an open heart. We measured the amplitude and duration of the complex **(fig. 12, 13)**.

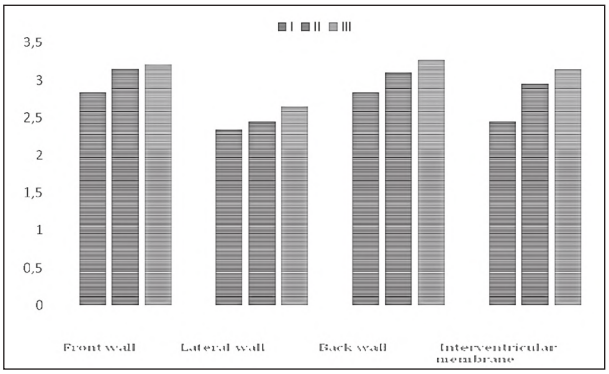

Figure 6 – Left ventricular wall thickness at different cross-sectional levels in (mm) in rats of the control and experimental groups (X±SD, n=27).

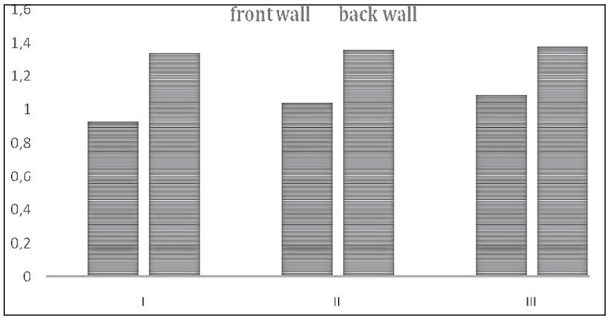

Figure 7 – The thickness of the heart's right ventricle wall at different levels of the transverse section in the control and experimental groups (in mm) (X±SD, n=27).

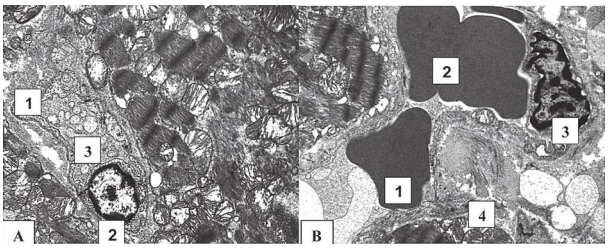

Figure 8 – Hemomicrocirculatory channel of the rat myocardium under conditions of general hypothermia. Electron micrograph. Magn.: ×3,000. Designation: A – 1- perivascular edema is visualized, 2 – multiple extracellular vesicles in the microcapillary lumen, 3 – swelling of the mitochondrial cristae apparatus; B – 1 – capillary, 2 – sludge syndrome of erythrocytes, 3 – endotheliocyte, 4 – myocardial stroma components.

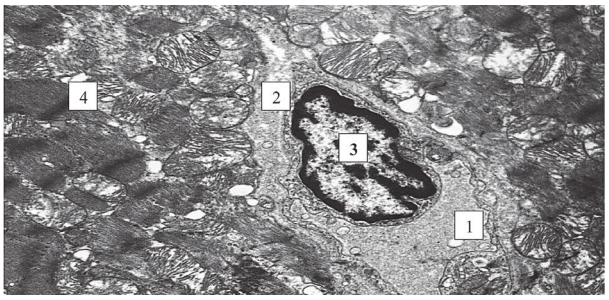

Figure 9 – Hemomicrocirculatory course of the rat myocardium under conditions of general hypothermia. Electron micrograph. Magn.: ×3,000. Designation: 1 – capillary, 2 – moderate perivascular edema, 3 – endotheliocyte, 4 – cardiomyocyte.

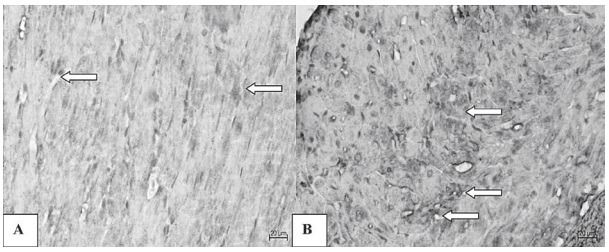

Figure 10 – Rat myocardium on the 30th day of the LC3B experiment. An arrow indicates areas of accumulation. Hematoxylin – eosin staining. Magn.: ob. 40. approx. 4.

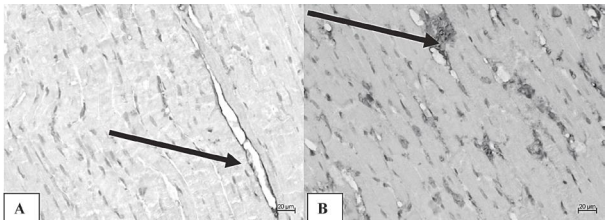

Figure 11 – Rat myocardium on the 30th day of the e NOS experiment. An arrow indicates areas of accumulation. Hematoxylin – eosin staining. Magn.: ob. 40. approx. 4.

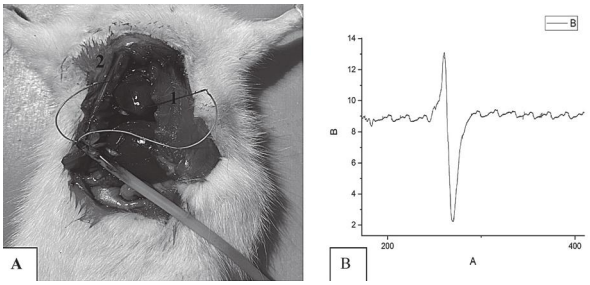

Figure 12 – Removal of the action potential from the heart with two-needle electrodes directly into the heart: A -1 at the top, 2 – at the base; B – ECG on an open heart is normal.

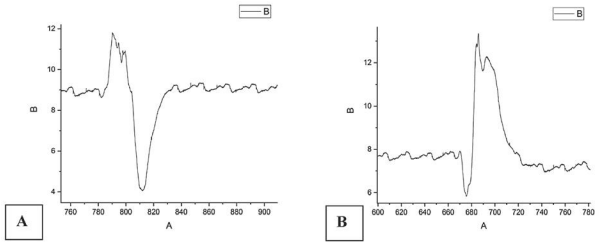

Figure 13 – ECG 10 – and (A) and 30 – and (B) days of general hypothermia.

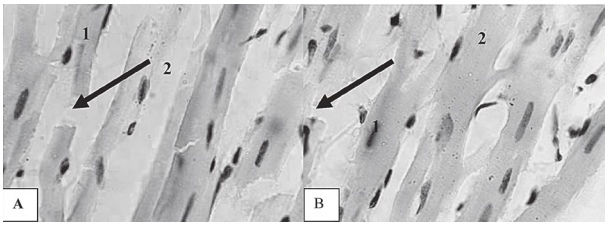

Figure 14 – Effect of local hypothermia (places with muscle fiber tears are indicated by arrows). Staining haematoxylin-eosin. Magn.: A, B-okh10; obh100. Designation: 1 – cardiomyocytes, 2 – intermuscular space.

When studying the effect of local hypothermia on histological sections of the myocardium of rats whose hearts were in a cardioplegic solution, the ventricular myocardium was represented by three layers of muscle fibers. The structure of cardiomyocytes and blood vessels did not differ from the control group. Cardiomyocytes are of the correct shape, and the spaces between cardiomyocytes are not enlarged.

Myocardium was damaged on histological sections of rats whose hearts were exposed to dry cold. There was muscle defibrillation, significant gaps between them, irregularly shaped cardiomyocytes, and deformed elements formed in the lumens of vessels. In some places, muscle fiber breaks **(fig. 14 A, B)**.

Conclusions. At the microscopic level, after the effect of general hypothermia with a duration of exposure of 10 days, an increase in the size of cardiomyocytes, the interstitial space was found, which indicated the activation of adaptive processes of the microcirculatory bed and the energy supply apparatus of cells that occur in cardiomyocytes under the effect of general hypothermia with an early duration of action; with a term of action of 30 days – marked defibrillation of muscle fibers in the myocardium of the heart of the ventricles and the interventricular membrane of rats. The effect of local hypothermia using a cardioplegic solution for cooling the heart allows you to preserve the typical structure of the myocardium, while protecting the structural organization. Dry cooling of the heart causes destructive changes in the myocardium with the development of degenerative and destructive processes in the myocardium of the heart, in places muscle fiber breaks, myofibrils defibration, their destruction and an increase in intercellular spaces, which indicates the depressing effect and irreversible damage of this method of local hypothermia (dry cold) on the myocardium of the ventricles and interventricular membrane.

Prospects for further research. It is planned to investigate ultramicroscopic changes in the myocardium of the heart wall under conditions of hypothermia.

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МОРФОФУНКЦІОНАЛЬНІ ЗМІНИ МІОКАРДА ЩУРІВ ПІСЛЯ ДІЇ ЗАГАЛЬНОЇ ТА МІСЦЕВОЇ ГІПОТЕРМІЇ

Кошарний В. В., Нефьодова О. О., Рутгайзер В. Г., Абдул-Огли Л. В., Козловська Г. О., Великородний В. І., Козловська О. Г.

Резюме. Метою дослідження було вивчення змін міокарда при дії загальної та місцевої гіпотермії на різних рівнях структурної організації.

Результати проведених досліджень дали змогу виявити загальні закономірності патологічних незворотних змін у стінці серця після дії місцевої гіпотермії у сухому холоді, після дії якого виникає виразне ушкодження м'язових волокон з їх розривами, а також з'ясувати, що після впливу місцевої гіпотермії у кардіоплегічному розчині мікроскопічно міокард шлуночків та міжшлуночкової перетинки не змінюється. Міжклітинний простір між окремими кардіоміоцитами збільшений. Ядра овальної форми в більшості кардіоміоцитів розташовані переважно у центрі клітин, у деяких зміщені до периферії. У внутрішньому шарі міжклітинний простір між сусідніми кардіоміоцитами більше, ніж у зовнішньому шарі. На гістологічних зрізах виявлено гіперемовані судини, ендотелій дрібних судин і капіляри набряклі. На ультраструктурному рівні виявлено переваскулярний набряк, набряк апарату крист мітохондрій, сладж синдром еретроцитів. В кардіоміоцитах відзначається набряклість саркоплазми особливо в зоні контакту з капілярами. Іноді зустрічалися мітохондрії гігантських розмірів за рахунок різкого набряку матриксу. Новостворені мікромітохондрії на тлі деструктивно-дегенеративних процесів виявлялися в невеликій кількості у вигляді дрібних сферичних утворень з поодинокими кристами, переважно поблизу ядра. У структурі зовнішньої мітохондріальної мембрани пошкоджень не спостерігалося. У просторах між міофібрилами переважали мітохондрії з ознаками структурно-функціональної перенапруги. Поряд з цим у великій кількості спостерігалися численні новостворені мікромітохондрії.

Виявлені зміни свідчать о ремоделюванні мікроциркуляторного русла та апарату енергозабезпечення клітин, що у сукупності свідчать про активацію адаптивних процесів що виникають в кардіоміоцитах під дією загальної гіпотермії.

Ключові слова: серце, міокард, загальна гіпотермія, місцева гіпотермія, імуногістохімія, електронна мікроскопія, електрофізіологічне дослідження.

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Kosharnyi V. V., Nefedova O. O., Rutgeiser V. G., Abdul-Ogly L. V., Kozlovska G. O., Velikorodny V. I., Kozlovska O. G.

Abstract. The aim of the study was to study changes in the myocardium under the action of general and local hypothermia at different levels of structural organization.

The results of the research made it possible to reveal the general regularities of irreversible pathological changes in the heart wall after the effect of local hypothermia in dry cold, after the result of which there is pronounced damage to muscle fibers with their ruptures, and also to find out that after the effect of local hypothermia in a cardioplegic solution microscopically, the myocardium of the ventricles and interventricular membrane does not change. Our studies of the myocardium of the heart wall of rats using transmission electron microscopy showed that the use of this method allows us to assess the processes of remodeling the heart after hypothermia and confirm the completeness of the structure of the studied objects.

The intercellular space between individual cardiomyocytes is increased. The oval nuclei in most cardiomyocytes are located mainly in the center of the cells, in some they are displaced to the periphery. The intercellular space between adjacent cardiomyocytes is larger than in the outer layer. On histological sections, hyperemic vessels, endothelium of small vessels and swollen capillaries were found. At the ultrastructural level, perevascular edema, edema of the mitochondrial cristae apparatus, erethrocytic sludge syndrome were revealed. In cardiomyocytes, swelling of the sarcoplasm is noted, especially in the zone of contact with the capillaries. There were few intermitochondrial contacts. Intermyofibrillar mitochondria were large, with moderately developed cristae and a transparent matrix. Among such organelles, organelles with elements of crystallization and zones of sharp enlightenment predominated. matrix.

The revealed changes indicate the microcirculatory bed and the cell energy supply apparatus in aggregate indicate the activation of adaptive processes arising in cardiomyocytes under the influence of general hypothermia.

Key words: heart, myocardium, general hypothermia, local hypothermia, immunohistochemistry, ultrastructure, electron microscopy, electrophysiological study.

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SUBMICROSCOPIC CHANGES IN THE SENSORIMOTOR AREA OF THE CEREBRAL CORTEX UNDER THE CONDITIONS OF EXPERIMENTAL HYPERHOMOCYSTEINEMIA, HYPER- AND HYPOTHYREOSIS AND THEIR COMBINED INFLUENCE

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Thyroid hormones (TH) play essential roles in growth and metabolic homeostasis in both humans and animals. In intrauterine life, provide temporal signals for the induction of differentiation and maturation programs at certain stages of fetal development. Among other things, THs regulate neuron plasticity processes, stimulate angiogenesis and neurogenesis, and also modulate the dynamics of cytoskeleton elements and intracellular transport processes. Homocysteine (HCy) is considered a risk factor for vascular diseases and brain atrophy. High levels of HCy have been found to promote increased oxidative stress, DNA damage, initiation of apoptosis, and excitotoxicity, all important mechanisms of neurodegeneration. HCy is also prothrombotic and proatherogenic and causes damage to the vessel wall, causing brain atrophy in the elderly. In addition, epidemiological data confirm that HCy is a risk factor for cognitive impairment and Alzheimer's disease.

The study aimed to establish submicroscopic changes in the cerebral cortex's sensorimotor area under experimental hyperhomocysteinemia, hyper-, and hypothyroidism and their combined effects.

Thiolactone HHCy was modeled by administering to animals exogenous homocysteine (HCy) in the form of thiolactone at a dose of 100 mg/kg of body weight once a day for 28 days. Hyperthyroidism was modeled by daily administration of L-thyroxine at a dose of 200 μg/kg during the 21 day, hypothyroidism by daily administration of mercazolil at a dose of 10 mg/kg during the 21 day. Separate groups of animals were injected with L-thyroxine and mercazolil in parallel with HCy.

HHCy was accompanied by destructively changed organelles and submicroscopic changes in astrocytic glia and blood capillaries. In turn, hyperthyroidism has caused hypertrophy of mitochondria, a decrease in the number of ribosomes, and destructive changes in hemocapillaries. The most significant alterative and degenerative changes in neurocytes of the cortex of the large hemispheres under hyperthyroidism and HHCy were established. Submicroscopically, the most profound violations of their ultrastructure were found in the neurons of animals modeled with HHCy and hypothyroidism compared to all previous observation groups.

Conclusions: submicroscopic studies of the sensorimotor cortex of the cerebral hemispheres of experimental groups under conditions of simulated HHCy, hypo- and hyperthyroidism, and especially under conditions of their combined influence, established profound submicroscopic neurodegenerative changes in the cerebral cortex. Established neurodegenerative changes in cortical neurocytes occur against neurovascular disorders' background and neuroglia's alteration.

Key words: *hyperthyroidism, hypothyroidism, hyperhomocysteinemia, the cerebral cortex.*